First NCI Epidemiology Leadership Workshop: Tobacco, Diet, and Genes

NATIONAL® CANCER INSTITUTE

Division of Cancer Control & Population Sciences

Epidemiology, "Large Science" and Consortia: Challenges and Opportunities

Daniela Seminara, PhD, M.P.H.

NATIONAL® CANCER INSTITUTE

Division of Cancer Control & Population Sciences

GOALS

- Define the "Large Science/Team Science" integrated concept and how it applies to epidemiological research

- Describe EGRP's experience in fostering and supporting epidemiology consortia and infrastructures

- Identify past and current challenges and propose possible solutions (based on experience from familial consortia)

NATIONAL® CANCER INSTITUTE

Division of Cancer Control & Population Sciences

Definition of "Large Science"…..Not so Clear-cut

"Characteristics of scientific research…vary along a continuum that extends from traditional, independent small scale research through very large, collaborative projects"

And, because of their characteristics "…new large-scale research opportunities are challenging traditional academic research structures" and funding agencies.

Large Scale Biomedical Science: Exploring strategies for Future Research;
Committee on large scale science and cancer research, IOM Report, 2003, Adapted

Very large-scale collaborative research characteristics

(and their pertinence to consortial efforts in epidemiology)

- Broad goals, sometimes encompassing an entire field of inquiry (i.e. genetic epidemiology of cancer)
- Problem-directed, with definable deliverables and endpoints
- Long-range strategic planning, longer time frame
- High initial infrastructure cost, high cost-efficiency
- Develops scientific research capacities, infrastructures and technologies that can be used by single-investigators projects
- Because of financial and intellectual investment, acceptance of concept by funding agencies and by the field essential
- Increased oversight by funders (U01s and similar mechanisms)
- Complex management structure, multi-investigators and multi-institutional groups
- Requires extensive bioinformatics support
- More interdisciplinary

NATIONAL® CANCER INSTITUTE

Division of Cancer Control & Population Sciences

Interdisciplinary Research/Team Science

- Teams are working in synergy at solving a complex scientific problem and developing related applications

- Exchange of concepts, approaches and intellectual discourse produces results beyond these possible with single-discipline approaches

- Areas of interface frequently characterize new sub-disciplines (i.e. epidemiology+genetics+molecular sciences+genomics = genetic, molecular epidemiology)

NIH roadmap, http://nihroadmap.nih.gov/interdisciplinary/index.asp

A fundamental assumption

To efficiently seek the answers to complex scientific questions within the population science framework of epidemiological studies, "large science" and "interdisciplinary research" must be seen as interrelated and complementary concepts that will be intrinsic to future epidemiologic research.

NATIONAL CANCER INSTITUTE

Division of Cancer Control & Population Sciences

Large Scale/Team Science in Epidemiology

- Question: role of gene-environment interplay in cancer development (comprehensive interpretation)
- Approach: interdisciplinary consortia (retrospective and prospective) within an epidemiology framework allowing flexibility of design
- Infrastructure requirements: large,well ascertained populations, integration of cutting edge genomic/molecular technologies; complete exposure, outcome,clinical and molecular assessment, informatics platform

Consensus Building…

- *"Genetic Epidemiology of Cancer: an Interdisciplinary Approach" Seminara, D. Obrams I. Genet Epidemiol. 1994;11(3):235-54*

  The final panel unanimously recognized that the understanding of how environmental and inherited factors interact in the etiology of cancer requires a **substantial integration of multi-disciplinary expertise and pooling of resources in a cost effective and productive manner**

- **Why Have We Failed to Find the Low Penetrance Genetic Constituents of Common Cancers? Neil E. Caporaso, Cancer Epidemiology Biomarkers & Prevention Vol. 11, 1544-1549, December 2002**

  Epidemiological studies that intend to evaluate genes must be of substantial size. **Diverse studies of various (i.e., both case-control and cohort) but sound design** will be required, as verification in different populations and exposure settings will be important. Because population differences in both exposure and genes will be considerations, **international cooperation will be a priority. Networking studies and consortia will be critical to encourage interdisciplinary and international participation.** Leaders must craft incentives into the granting structure to reward such cooperation

- **Joseph Fraumeni, M.D., Cancer and the Environment, Institute of Medicine, 2002**

  "The big challenge for epidemiology now is to develop strategies to ensure that the **advances in human genomics are incorporated appropriately into population studies, as well as family-based, and hybrid studies.**"

- **Consortia "Big Science" Part of a Paradigm Shift for Genetic Epidemiology Karen Kreeger, JNCI, 95, 9,**

NCI Continued Interest in, and Support of Large, Interdisciplinary Epidemiology

NATIONAL® CANCER INSTITUTE

Division of Cancer Control & Population Sciences

NIH Bypass Budget 2005

Core Research Areas "Genes and the Environment": particular attention to epidemiologic consortia
(http://plan.cancer.gov/genes.html)
Addressing Areas of Public Health Emphasis: Tobacco and Tobacco-Related Cancer
http://plan.cancer.gov/tobacco.html
Optimizing Energy Balance to Reduce the Cancer Burden
http://plan.cancer.gov/energy.html

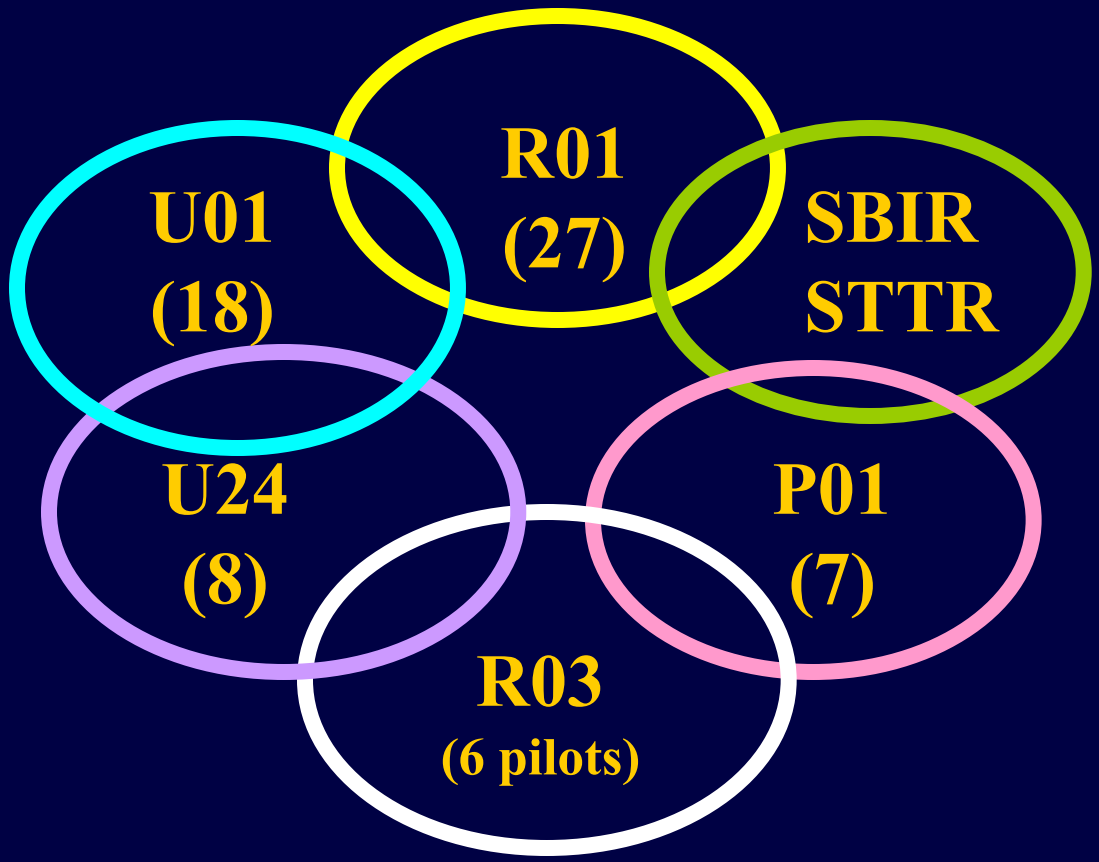
NIH Bypass Budget 2004

Building the Nation's Cancer research Capacity: Expanding the Capacity of Networks, Centers and Consortia
http://plan2004.cancer.gov/capacity/centers.htm
Advancing Discoveries and its Application: Genes and the Environment (particular attention to consortia) http://plan2004.cancer.gov/discovery/genes.htm
Addressing Areas of public Health Emphasis: Tobacco and Tobacco-Related Cancer
http://plan2004.cancer.gov/discovery/genes.htm

How does the Epidemiology and Genetics Research Program (EGRP) Foster Consortia?

- Identify research priorities
- Assess needs
- Provide resources, coordination and communication among participating groups and with other consortia
- Facilitate and expedite research implementation and translational process
- Evaluate performance: in cooperation with investigators, develop milestones and “best practices”
- Involvement in planning and research (cooperative agreements and contracts)

A Range of Complementary Mechanisms is Available to Support Interdisciplinary Consortia in Epidemiology



Team Science Identified Needs
(from: NIH Roadmap http://nihroadmap.nih.gov/)

- Support from *multiple* NIH ICs—especially for projects not primarily related to any one IC
- Appropriate *credit* to key investigators, key institutions and NIH funders
- Project *management* by skilled grantees
- Project *oversight* by all NIH funders
- Allow for *evolution* of team effort in directed and serendipitous ways

New Consortium Model: Basics

- Applicants bundle together grant applications, each focused on a specific aspect of team effort
- Number and types of mechanisms comprising each consortium would depend on needs of that team effort. Grants must interact highly to add synergy to the consortial effort.
- Each consortium would be *required* to have a Project Leadership and Management grant, headed by an eminent scientist who could articulate the vision and science of the team effort. No research supported by this grant

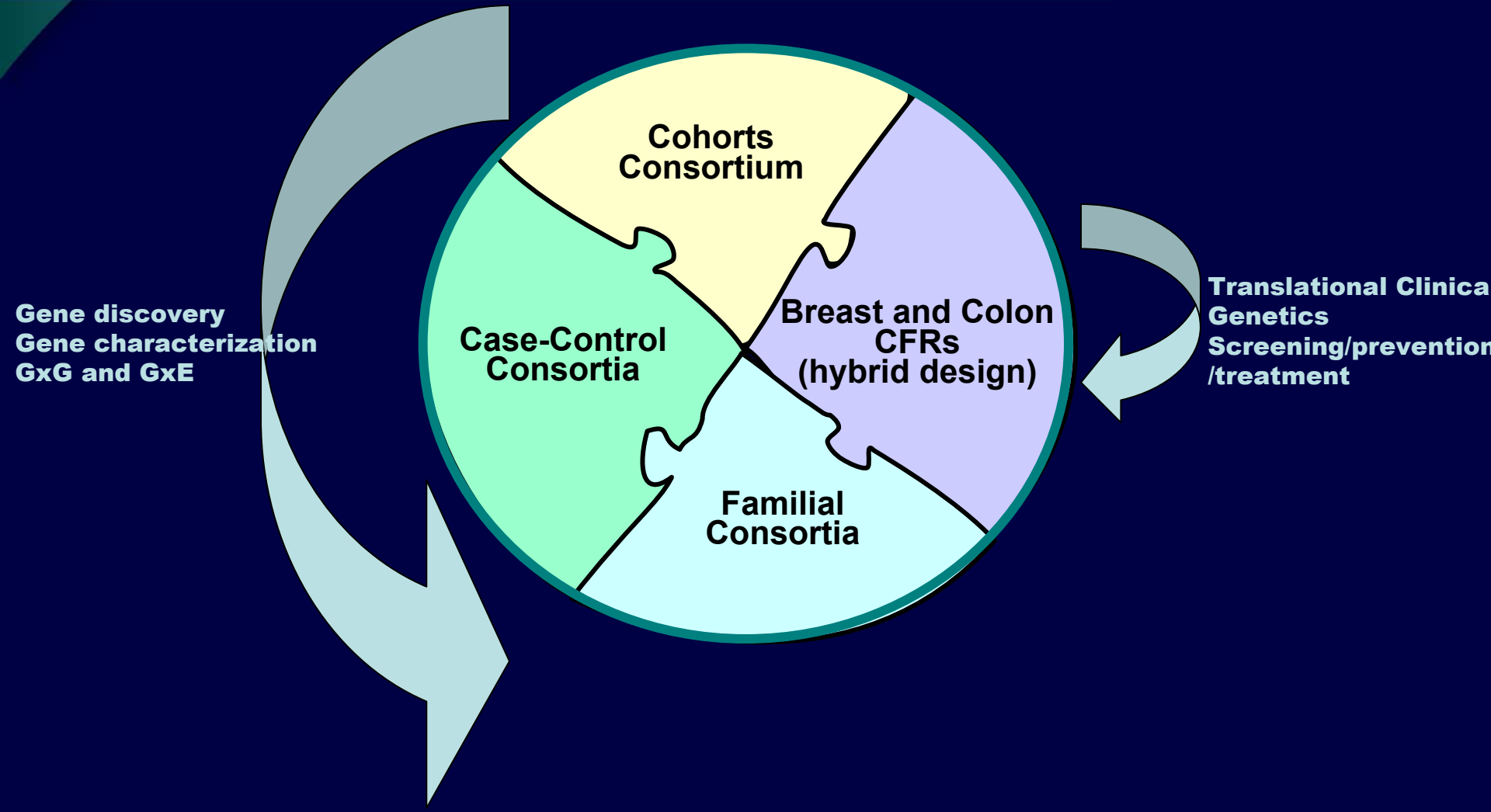
New Consortium Model: Evolution

- Consortial Grants RFAs might be issued to solicit additional grant applications to join particular consortia as integral parts. These would be reviewed in the context of that consortium
- Satellite Grants Grants affiliated only by scientific serendipity would also be able to become affiliated to consortia. These would not be considered integral parts of a consortium
- Grantees would be expected to understand that continued support depends on progress of each grant and achievement of consortial goals
- Oversight would be by a cross-institutes extramural team

EGRP- Supported Epidemiology Consortia: Flexibility of Design

NATIONAL CANCER INSTITUTE

Division of Cancer Control & Population Sciences



NATIONAL CANCER INSTITUTE

Division of Cancer Control & Population Sciences

Research Infrastructures Hybrid Design

- The Breast and Colon Cancer Family Registries*

http://epi.grants.cancer.gov/CFR/

Contact: Daniela Seminara, seminard@mail.nih.gov

- The Cancer Genetics Network (Phase-out)**

http://epi.grants.cancer.gov/CGN/

Contact: Carol Kasten-Sportes, kastenca@mail.nih.gov

*Family, case-control and hybrid designs

** Screening, clinical trials

Breast, Ovarian and Colorectal Cancer Family Registries (BC-CFR)

NATIONAL® CANCER INSTITUTE

Division of Cancer Control & Population Sciences

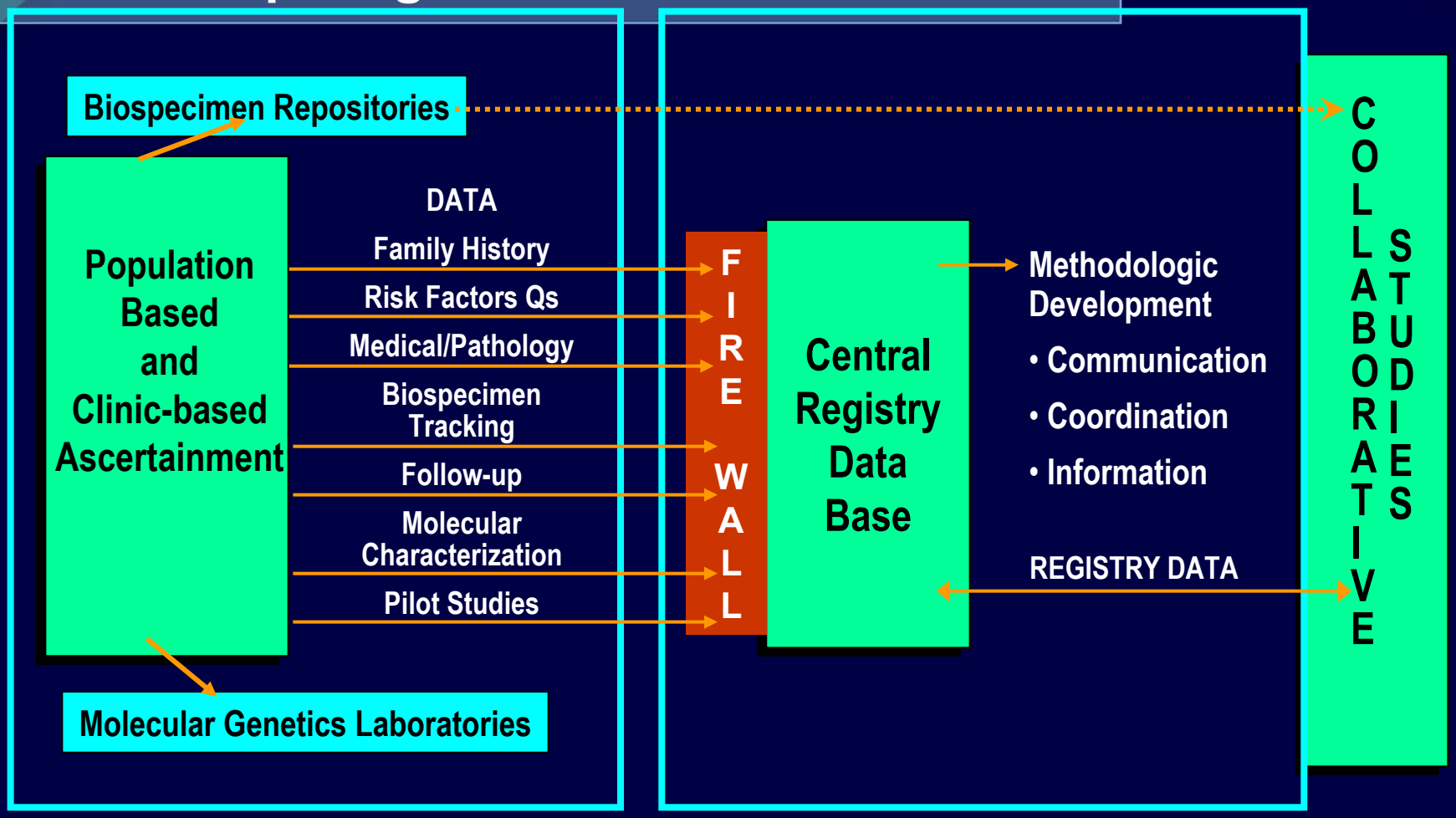
Goals

Ascertain, characterize and follow up a familial cohort spanning the whole spectrum of cancer risk, and establish a comprehensive familial infrastructure for the implementation of collaborative, interdisciplinary research protocols in the genetic epidemiology of cancer

Identify subpopulations at higher cancer risk that could benefit from enrollment in preventive and therapeutic interventions

Contribute to the development of effective Public Health measures by increasing knowledge of the genetic factors affecting cancer susceptibility and their interaction with modifiable environmental and lifestyle factors (general population).

BC-CFRs Design



NATIONAL CANCER INSTITUTE

Division of Cancer Control & Population Sciences

BC-CFR
Why an Unique Infrastructure?

- Largest and best characterized collection of breast and colon cancer population-based families in the world
- Population- and clinic-based ascertainment and population-based controls = *design flexibility*
- Extensive biospecimen collection with related risk factors data = *high-throughput molecular technologies and gene-environment studies*
- Driven by an interdisciplinary research agenda = *adapts to advances in knowledge*

NATIONAL® CANCER INSTITUTE

Division of Cancer Control & Population Sciences

Access to Collaborative Research

- Proposal for collaborative protocols are strongly encouraged from national and international groups with appropriate expertise.

- Access requires formal application. Information at http://www.cfr.epi.uci.edu/

- CFRs tools and protocols are available

Familial Consortia (Clinics)

National Cancer Institute
Division of Cancer Control & Population Sciences

- Genetic Epidemiology of Lung Cancer (GELC)
- International Melanoma Consortium (familial component)
- International Consortium on Prostate Cancer Genetics (ICPCG)
- Pancreatic Cancer Genetic Epidemiology Network (PACGEN)
- Chronic Lymphocytic Leukemia Familial Consortium ★
- Multiple Myeloma Familial Consortium ★
- Lymphoprolypherative Cancers Familial Consortium ★
- Brain Tumor Consortium (familial component) ★

★ Newly formed

Contact: Daniela Seminara, seminard@mail.nih.gov

NATIONAL CANCER INSTITUTE

Division of Cancer Control & Population Sciences

Case-Control Consortia

- Interlymph (lymphomas)
- Molecular Epidemiology of Colorectal Cancer (MECC)
- International Lung Cancer Consortium ★
- Head and Neck Cancer Consortium ★
- International Melanoma Consortium (case-control component)
- Brain Tumors Consortium (case-control component) ★
- Genetic Epidemiology of Melanoma (GEM)
- Breast Cancer, Radiation Exposure and Cancer Susceptibility Genes (WE CARE)
- Bladder Cancer ★

★ Newly formed

Information: http://epi.grants.cancer.gov/Consortia/casecontrol.html

Cohort-related Activities

- **EGRP currently supports numerous large cohorts around the world** http://epi.grants.cancer.gov/ResPort/cohorts.html *Contact: Sandra Melnick, melnicks@mail.nih.gov*

- **The Cohort Consortium was formed by NCI (EGRP/DCEG) to address the need for large-scale collaborations for study of GxG and GxE interactions in the etiology of cancer. General cohort studies worldwide with >10,000 subjects, blood samples (including white blood cells) and questionnaire data on important cancer risk factors were invited to participate.**

- **10 of these cohort are currently involved in a collaborative study of GxE interactions in breast and prostate cancer**

- **A similar large study of pancreas cancer is in the planning stage and other "spin-off" studies are anticipated**

Consortia/Team Science for the next generation?

NATIONAL CANCER INSTITUTE

Division of Cancer Control & Population Sciences

insight commentary

The case for a US prospective cohort study of genes and environment

Francis S. Collins

National Human Genome Research Institute, National Institutes of Health, Building 31, Room 4B09, MSC 2152, 31 Center Drive, Bethesda, Maryland 20892-2152, USA (e-mail: fc23a@nih.gov)

Information from the Human Genome Project will be vital for defining the genetic and environmental factors that contribute to health and disease. Well-designed case–control studies of people with and without a particular disease are essential for this, but rigorous and unbiased conclusions about the causes of diseases and their population-wide impact will require a representative population to be monitored over time (a prospective cohort study). The time is right for the United States to consider such a project.

Cancer Epidemiology Biomarkers & Prevention Vol. 13, 895-897, June 2004

Toward the Last Cohort - John D. Potter

Fred Hutchinson Cancer Research Center, Seattle, Washington

"… a study of a very large number of ethnically diverse individuals who are well characterized genetically, whose exposures are diverse and well mapped, and whose illness pattern and mortality can be monitored…to attempt to establish the complete pattern of human disease susceptibility and resistance, to establish longitudinal profiles as early-detection markers, and to identify more precise phenotypes.This cohort, if we do it correctly, could be "The Last Cohort".

And Even Further: Youth Cohorts

NATIONAL CANCER INSTITUTE

Division of Cancer Control & Population Sciences

***The Breast Cancer and the Environment Research Centers Cohort Study on Environmental and Genetic Determinants of Puberty**

- Investigate the determinants of thelarche and sexual development studies in young girls from diverse ethnic/racial backgrounds
- Explore the role of relevant epidemiologic risk factors to future breast cancer risk, and social factors on outcomes related to puberty
- Collect and bank DNA samples for future use
- Utilize information from Collaborative Projects 1(Effects of Environmental Exposures on the Molecular Architecture of the Mammary Gland over the Lifespan) to determine which gene X environment hypotheses would be worth pursuing

***The Breast Cancer Family Registries LEGACY Study (pilot): a cohort of children of the enrolled breast cancer families**

Prospective and Retrospective Consortia in Epidemiology: Different Models, Similar Challenges…

NATIONAL® CANCER INSTITUTE

Division of Cancer Control & Population Sciences

CHALLENGES	POSSIBLE SOLUTIONS
Informed consent and IRBs' variable behaviors	Prospective consortia, re-consent, IRBs'education (ICPCG)
Informatics and analytic support for collection, management and analysis of extremely large and complex datasets sets	Central informatics units, standardization of informatics platform (caBIG), "think tank for analytic challenges of already collected datasets
Rapid and continuous integration of cutting-edge genomic and other technologies	Centralized technology platforms, public-private partnership
Biorepositories: centralized versus local, large scale retrieval of tissue	Work toward maximizing bioresources (transformed cell lines, whole genome amplification, pooling, tissue microdissection, multiplex microarrays)
Integration of disciplines: most institutions house scientists in discrete departments and work from different operating cultures. NIH Institutes focus on single outcomes	Interdisciplinary training and lexicon, integration of new knowledge and concepts as they arise, shift in academic culture triggered by multiple outcome funding approaches by NIH Institutes

NATIONAL® CANCER INSTITUTE

Division of Cancer Control & Population Sciences

…and More

CHALLENGES	POSSIBLE SOLUTIONS
Intellectual property rights	Carefully crafted agreements, involving all partners
Authorship and principal investigatorship (especially for young investigators). The current system of academic advancement favors the independent investigators	Change in structure of funding mechanisms, tenure criteria, publication credits.
Access for the scientific community at large	Development of clear process and policies (I.E. CFRs), NIH may help with cost of sharing data
Review Process	Appropriate IRG, education of peer scientists Interdisciplinary science requires interdisciplinary peer-review
Interdisciplinary research teams take time to assemble and require unique resources	Appropriate criteria for evaluation and measure of productivity taking in account planning and time to establish Infrastructure. Evaluate core activities and tools developed

Single Project – Single Investigator Paradigm

Consortia/Team Science: A new Paradigm to Address Complex Questions in Epidemiology